REMARKS

The above amendments to the above-captioned application along with the following remarks are being submitted as a full and complete response to the Official Action dated April 6, 2005. In view of the above amendments and the following remarks, the Examiner is respectfully requested to give due reconsideration to this application, to indicate the allowability of the claims, and to pass this case to issue.

Status of the Claims

Claims 3, 5-7, 14-15, and 23 are under consideration in this application. Claims 3, 5-7, 14-15, and 23 are being amended, as set forth above, in order to more particularly define and distinctly claim Applicants' invention. Applicants hereby submit that no new matter is being introduced into the application through the submission of this response. In particular, the amendments to claim 26 "along a circumferential path on a ~~cylindrical~~ plane" is supported by page 13, last paragraph of the specification, and the amendments to claims 14-15 "on a three-dimensional gene map of a gene ~~on a gene map~~ that causes the expression phenomenon" is depicted in Fig. 5. The amendments to all independent claims "a database that collects ~~memorizes~~", and the amendment to claims 14-15 "~~coordinating~~ organizing" are supported by the dictionary definition of the respective words.

Formality Rejection

Claims 3, 5-7, 14, 15 and 23 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the recitation of "a database that memorizes," "coordinating and displaying," "gene map that causes the expression phenomenon," and "cylindrical plane." As indicated, the claims have been amended as suggested or required by the Examiner. Accordingly, the withdrawal of the outstanding informality rejections is in order, and is therefore respectfully solicited.

Allowable Subjected Matter

Applicants note that there are no pending prior art rejections against claims 14-15 and 23, and these claims were only rejected under 35 U.S.C. § 112, second paragraph. As

these claims have been amended to overcome the 112 rejections, they are believed to be in condition for allowance.

Prior Art Rejections

Claims 3 and 5 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the article of Hartenstein et al., *Trends in Genetics,* 1995 ("Hartenstein") in view of US. Pat. No. 6,096,510 to Hochman (hereinafter "Hochman"), and against claims 6 and 7 as being unpatentable over Hartenstein in view of US. Pat. No. 6,308,170 to Balaban (hereinafter "Balaban"). These rejections have been carefully considered, but are most respectfully traversed.

The method for displaying a gene expression phenomenon in one or more living organisms (e.g., p. 3, line 3: human; p. 13, last line: Ascidian/sea squirt[1]) in a system comprising a database that collects, for each cell or each site (e.g., "*a lung or a liver*" p. 16, line 22) of said living organisms along a time axis, data indicative of a shape of said cell or site and expression data associated with a degree of expression of the gene expression phenomenon in said cell or site along a time axis; and processing means adapted to obtain said data indicative of the shape and expression data that are collected in said database to visualize and display the gene expression phenomenon on a display screen, as now recited in claim 3, comprises: a first step of displaying as a three-dimensional image on the display screen a shape of said living organisms of which the gene expression phenomenon is observed; a second step of setting a viewpoint by a user via a keyboard 202 or a mouse 203 (Fig. 2; "*the keyboard 202 or the mouse 203 associated with the computer 201 may be used to designate a site of a living matter, designate a cell, or the designate the viewpoint of an observer*" p. 38, 2nd full paragraph) on a three-dimensional space where the gene expression phenomenon in said living organisms displayed is to be observed; and a third step of reading the gene expression data of said cell or site of said living organisms out of said database, creating a plurality of three-dimensional images representing the gene expression phenomenon at the viewpoint set at said second step or at a fixed viewpoint, to display at least one of said

[1] AHox1 is an Ascidian (*Halocynthia roretzi*/ sea squirt) homeobox gene; AMD1 is an Ascidian gene developed into body wall muscle in adult stage; and As-T is an ascidian homologue (As-T) of the mouse T gene.

three-dimensional images in multiple tones using one color or multiple colors, each of the tones corresponding to a degree of expression of the gene expression phenomenon.

In particular, the method includes a step of **simulating** gene expression data by analyzing actual gene expression data ("*the present invention is implemented to simulate development of an organism*" p.12, lines 17-18; "*simulates development of fertilized eggs*" p. 37, line 2; "*IntelligentBox" on which installed are a biological simulation program 2012 and a DB access program 2013 for accessing the gene DB 205*" p. 15, lines 7-9; "*An approach that covers these shortcomings includes an in vivo staining experiment technique to observe a real organism directly rather than through analysis of data [as the invention]* p. 2, 3rd paragraph") and chronologically displaying a simulated change in shape of said cell or site of said living organisms caused by an external stimulation (p. 37, lines 7-8; Fig. 37) artificially incurred by altering simulation parameters according to a planned experiment ("*the result of a planned experiment on a life form, rather than natural phenomena, can be visualized*" "*by altering the parameters*" p. 2, 1st paragraph of the previously submitted 132 declaration) **and** a change in shape of a cell or site caused by internal activities of said cell or site of said living organisms; and displaying an animation of a three-dimensional image representing the gene expression phenomenon from a certain viewpoint at a certain instant of time.

The biological simulation program 2012 uses the DB access program 2013 to assess the database ("*experimentally observed data*" p. 1, last paragraph)") and to create a mathematical model of a gene expression phenomenon in one or more living organisms, to visualize "simulated experiments" by extracting specific conditions from across the database resulting from observation and prior experiments under natural and artificially stimulated conditions. The invention shows how the gene expression phenomenon develops and, by changing variables, such as adding an external stimulation artificially incurred according to a planned experiment, make predictions about how the gene expression phenomenon will change. The invention enables three-dimensional visualization of the movement of specified gene groups by extraction in accordance with specific conditions from a database accumulated under various conditions, e.g., an external stimulation such as thermal change, environment composition change, addition of inorganic or organic chemical materials from outside, electrical stimulation, or miRNA (micro RNA that peculiarly inhibits the expression of a target gene). As shown in Fig, 28, "*the change in shapes of sites 2802, 2803, 2804, and 2805 is displayed along the time*

axis when the external simulation is applied to a living matter 2801 at the position designated by an arrow P (p. 34, last 4 lines of the paragraph beginning with Fig. 28)." As another example, when the database only contains the data of a first experiment involving an external stimulation A and the data of a second experiment involving an external stimulation B, the invention can simulates the change as if both external stimulation A and B were applied.

"Details of the IntelligentBox can be found in,.... Yoshihiro Okada and Yuzuru Tanaka, "Collaborative Environments of IntelligentBox for Distributed 3D Graphic Applications", Proceedings of the Computer Animation '97, IEEE Computer Society. Since processing and display of the three-dimensional graphics herein are completely based on the IntelligentBox system in this example, description about the process is omitted in this embodiment section (p. 15, lines 9-27)." An IDS of the four references are being concurrently filed with this response.

As described in the 1997 article, IntelligentBox provides a constructive visual software development system for interactive 3D graphic applications, which represents any objects as reactive 3D visual objects, which are called Boxes that can be manually combined with other Boxes. It provides a uniform framework for the concurrent definition of both geometrical compound structures among Boxes and their mutually interactive functional linkages. A collaborative environment is introduced as a function of a particular Box called a RoomBox for distributed 3D graphic applications. Multiple RoomBoxes on different computers share specific user-operation events with each other. An application example in Fig. 4 shows a composite box of a motor and tires.

In short, the invention provides a database interface which simulates and visualizes virtual experiments to prompt a user to come up with new knowledge and findings.

Applicants contend that neither Hartenstein nor Hochman teach or suggest "simulating gene expression data by analyzing actual gene expression data and chronologically displaying a simulated change in shape of said cell or site of said living organisms caused by an external stimulation artificially incurred by altering simulation parameters according to a planned experiment" as the invention.

Hartenstein discloses that gene expression data of Drosophila as a model organism in the stage of embryonic development is electrically stored in a three-dimensional graphical database. Hartenstein is basically directed to direct visualization

of natural life phenomena that have been observed and stored in the database. Hartenstein fails to shed any light on a gene expression network through the use of functions for, e.g., focusing on a network of specific genes and comparatively displaying the genes, or visually tracking the behavior of a particular group of genes under the binding conditions of a virtual experiment involving specific stimulations.

The present invention simulates and displays the simulated result of planned/virtual experiments on a life form, rather than just faithfully displaying natural biological phenomena or animations of embryogenesis as Hartenstein. The invention simulates/predicts gene expression data by analyzing actual gene expression data based upon an approximate (mathematical) model and applying existing data to IntelligentBox.

As admitted by the Examiner, "Hartenstein does not include situations involving artificially incurred external stimulation according to a planned experiment (p. 4, 4th paragraph of the outstanding Office Action)". Hochman is relied upon by the Examiner to teach such a feature. However, Hocman merely evaluates the physiological condition (col. 4, line 19), health condition, or growth capacity of biological material (such as cells, tissues, or internal organ) by analyzing optical signals. In other words, Hochman is directed to merely analyzing optically/actually observed signals, rather than simulating gene expression data by analyzing actual gene expression data and chronologically displaying a simulated change in shape of said cell or site of said living organisms caused by an external stimulation artificially incurred by altering simulation parameters according to a planned experiment.

The invention recited in claim 5 displays in parallel on the display screen three-dimensional images representing expression phenomena for each cell or site of said living organisms of **multiple species** (2901, 2902 in Fig. 29; 3001 and 3002 in Fig. 30; "*the cells of two living matters*" p. 35, 1st paragraph; p.3, line 3; p. 32, 2nd paragraph); comparing the three-dimensional images representing the gene expression phenomena for each cell or site of said living organisms of multiple species to visually display similarities therebetween in a predetermined display format.

The invention displays of not only the embryogenesis of a single type of living organism, but also a comparative display of the gene expressions of a plurality of living organisms three dimensionally so as to analyze what adaptations occur among gene networks in the process of evolution, and a difference in a gene network of gene groups which is responsible for the difference that leads to a species-specific branching. Also, as

compared with a method for visualizing the embryogenesis of a **single species**, the invention makes it possible to clarify a specialized role of a gene function in ontogenesis in higher dimensions by comparing the information being expressed in each site/organ. Visualizing **3D differences among multiple species** makes it possible to prove relationships between evolution and expression, so that functions of individual genes and their relations can be speedily discovered without conducting some experiments that are expensive or involve ethical problems.

As admitted by the Examiner, "Hartenstein does not teach displaying the gene expression phenomenon of multiple species (p. 4, 5th paragraph of the outstanding Office Action)". Hochman is relied upon by the Examiner to teach such a feature. Although Hocman tests and observes healthy, pathogenic and dysfunctional cells and tissue in situ in animal models (col. 3, lines 61-63), and compares various data sets, and/or control data profiles, to generate comparison data relating to changes in geometrical and/or optical properties indicative of changes in the physiological state of "sample populations". The same populations of the same species (rather than multiple species) are displayed on one display screen, for examples, Figs. 9A-B show time course and magnitude plots of dynamic optical changes just in human cortex evoked in tongue and palate sensory areas and in Broca's area (language), while Figs. 10A-D illustrate the cranial surface only of a rat, imaged through the intact cranium, and using a contrast enhancing agent to highlight areas of optical change.

Hochman is totally different from the present invention in terms of basic function, structure, or objectives, the concept of the latter being such that gene expression profiles are directly or indirectly digitized and stored in a database, which is then searched via a there-dimensional interface.

The invention recited in claim 6 maps three-dimensional images of a cell or site along a time axis to display the three-dimensional images in one color or multiple colors in various scales on one display screen depending on a *gene expression frequency* in said cell or site. See Fig. 26; p. 34, 1st full paragraph. The invention (**claim 7**) maps three-dimensional images of two or more cells or sites on coordination points along an axis to displays the three-dimensional image in one color or multiple colors in various scales of a *change in gene expression frequency* in said cells or sites in parallel. See Fig. 32; p. 35, 2nd to the last paragraph.

As admitted by the Examiner, "Hartenstein does not teach dmapping expression data along a time axis and mapping the expression data of two or more experiments (cells) on coordination points along an axis (p. 5, 4th and 5th paragraphs of the outstanding Office Action)". Balaban is relied upon by the Examiner to teach such features. However, Balaban compares gene expression profiles between tissues, diseases, internal organs, species, or the like, and only display comparative results via texts, tables, bar graphs, or 2D comparison charts, but not 3D images of a cell or site along a time axis in scales depending on a *gene expression frequency* or 3D images of two or more cells or sites on coordination points along an axis in scales of a *change in gene expression frequency*. Although Balaban employs a comprehensive database search mechanism, it does not enable a dynamic comparative display of specific gene groups in a **3D** space, as specified in claims 6-7. Also, Balaban does not disclose an interface for facilitating the gaining of knowledge or discovery through comparison and observation of gene expression states in accordance with morphological similarities.

The invention effectively displays the expression of a specified gene in a **3D** manner using three primary colors. This enables a dynamic display of the relationships among multiple genes, which was impossible by merely displaying a change in a single gene in terms of embryogenesis in chronological order. Thus, the sequence of events wherein an increase of expression of a certain gene brings about an increase or decrease of expression of another gene, which affects other factors, and so on, can be visualized. This effective method also supports the effects of claims 3 and 5.

Applicants contend that neither the cited references, nor their combination teaches or discloses each and every feature of the present invention as disclosed in independent claims 3 and 5-7. As such, the present invention as now claimed is distinguishable and thereby allowable over the rejections raised in the Office Action. The withdrawal of the outstanding prior art rejections is in order, and is respectfully solicited.

Conclusion

In view of all the above, clear and distinct differences as discussed exist between the present invention as now claimed and the prior art references upon which the rejections in the Office Action rely, Applicants respectfully contend that the prior art references cannot

anticipate the present invention or render the present invention obvious. Rather, the present invention as a whole is distinguishable, and thereby allowable over the prior art.

Favorable reconsideration of this application is respectfully solicited. Should there be any outstanding issues requiring discussion that would further the prosecution and allowance of the above-captioned application, the Examiner is invited to contact the Applicants' undersigned representative at the address and phone number indicated below.

Respectfully submitted,

Stanley P. Fisher
Registration Number 24,344

Juan Carlos A. Marquez
Registration Number 34,072

REED SMITH LLP
3110 Fairview Park Drive
Suite 1400
Falls Church, Virginia 22042
(703) 641-4200

July 5, 2005

SPF/JCM/JT